King Saud University

Journal of Saudi Chemical Society

www.ksu.edu.sa
www.sciencedirect.com

Journal of Saudi Chemical Society

ORIGINAL ARTICLE

Synthesis of new annulated pyrano[2,3-*d*]pyrimidine derivatives using organo catalyst (DABCO) in aqueous media

CrossMark

Ajmal R. Bhat [a], Aabid H. Shalla [b], Rajendra S. Dongre [a],*

[a] *Department of Chemistry, RTM Nagpur University, Nagpur 440033, India*
[b] *Islamic University of Science and Technology, Kashmir 192122, India*

Abstract A selective method for the synthesis of annulated pyrano[2,3-*d*]pyrimidines has been developed. It was shown that base catalysis is more efficient in this reaction, rather than acid catalysis as it is believed that 1,4-diazabicyclo[2.2.2]octane (DABCO) is N-type base catalyst used for the synthesis of pyrano[2,3-*d*]pyramidine derivatives via one-pot three component condensation reactions of various aromatic aldehydes, active methylene compounds and barbituric acid in aqueous ethanol carried at normal temperature. The potential application of DABCO in organic synthesis increasing rapidly because of its reaction simplicity, less pollution, and minimum reaction time, high yields of the biological active products, uses less toxic solvents and low cost chemicals.
© 2014 Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Multicomponent reactions (MCRs) have enormous benefit with their high yields of products, ease of execution in the aim of analysis of combinatorial chemistry [32]. However, in the past decade there has been tremendous development in three- and four-component reactions and great efforts were taken to develop new MCRs [29,7]. Solid-phase organic synthesis is a background of generating libraries of molecules for the discovery of biologically active leads and also for the optimization of potent drug molecules. Many organic solvents are harmful and their use should therefore be minimized as far as possible. Green alternatives under investigation for organic reactions are water [8,11], supercritical fluids, in particular CO_2 [19] and solvent-free condition (SFC) [23]. The use of water as the reaction medium exhibits a significant advantage because this green solvent is highly polar and therefore immiscible with most organic compounds [21]. Moreover the water-soluble catalyst resides and operates in the aqueous media, and separation of organic compounds is thus easy. Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, simple work up, comparatively cheaper to operate and particularly important in industry. Thus, there is a need for developing multicomponent reactions (MCR's) in aqueous ethanol and without the use of harmful organic solvent.

The synthesis of fused heterocycles has attracted considerable interest in heterocyclic chemistry as the fusion of biodynamic heterosystems has proved to be very attractive and constructive for the design of a new molecular framework of potential drugs with varying pharmacological activities. A major challenge of the modern synthetic chemistry is to design highly efficient chemical reaction sequences which provide molecules containing maximum complexity and structural diversity with interesting bioactivities in minimum number of synthetic steps. Recently, organocatalyst has increased extremely in the last few years as a result of both the novelty of the concept and, more importantly, the fact that the efficiency and the selectivity of many organocatalyst reactions meet the standards of established organic reactions. One of these organo catalysts is the 1,4-diazabicyclo[2.2.2]octane (DABCO) which has received considerable attention as an inexpensive, eco-friendly, high reactive and non-toxic base catalyst for various organic synthesis, affording the corresponding products in excellent yields with high selectivity. Pyrano[2,3-d]pyrimidine is unsaturated six membered heterocycle which is formed by fusion of pyran and pyrimidine rings together, consisting of one oxygen atom at position number 8 and two nitrogen atoms at position number 1 and 3 respectively. If pyrano[2,3-d]pyrimidine moieties are clubbed into one molecule, then resultant derivative enhances its pharmaceutical activity as abundant in biologically active compounds such as antitumour [2], cardiotonic [12], antibronchitic [17] and antifungal activity [26]. Some of them exhibit antihypertensive activity [6], antimalarial [9], analgesic [20,30]; and antiviral evaluation [27] properties. Pyrano[2,3-d]pyrimidines are building blocks used to evaluate their antimicrobial activities and various derived natural products are also used as a drug for insomnia treatment [24]. Therefore, for the preparation of these complex molecules large efforts have been directed toward the synthetic manipulation of pyrano[2,3-d]pyrimidine derivatives. As a result, a number of reports have appeared in the literature which usually requires forcing conditions, long reaction times and complex synthetic pathways. Pyrano[2,3-d]pyrimidine synthesis was reported under various conditions such as microwave irradiation [10,13], ultrasonic irradiation [18], solvent free condition and in aqueous medium in the absence of catalysts [14]); sulfonic acid nanoporous silica (SBA-Pr-SO$_3$H) [34], diammonium hydrogen phosphate (DAHP) [3], L-proline (Heravi et al., 2010); [5], H$_{14}$[NaP$_5$W$_{30}$O$_{110}$] (Heravi et al., 2010), ionic liquids [33]. Reported methods appearing in the literature usually require forcing conditions, long reaction time, create wastes, need complex synthetic pathway and involved organic solvents as well high energy to proceed. So, due to environmental concerns associated with aspects of organic solvents, development of aqueous phase synthesis of pyrano[2,3-d]pyrimidines is of considerable interest in this research to cater short reaction

time, environmentally friendly procedure and excellent yields by this proposed route. Aqueous ethanol (ethanol:water) in place of organic solvents was used besides being non-hazardous, it is cheap, readily available and simple to handle so, we describe here a rapid, energy efficient, green and economically viable and easy (room temperature) protocol for the synthesis of pyrano[2,3-d]pyrimidine derivatives by using DABCO catalyst (Scheme 1).

2. Materials and methods

All chemicals were obtained from Aldrich Chemical Co. and S.D. Finechem Co. and used without further purification. Melting points were determined by open capillary method and were uncorrected. ^{1}H NMR spectra were obtained on a BRUKER instrument (300 MHz). IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer using KBr pellet and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6 as solvent with TMS as internal standard. Chemical shifts are reported in ppm and mass spectra were measured using high resolution GC–MS (DFS) thermo spectrometers with EI (70 EV). Reactions have been monitored by thin layer chromatography on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365 nm) or with an iodine vapor Scheme 2).

2.1. General procedure for the preparation of pyrano[2,3-d]pyrimidinones

Aromatic aldehydes (**1**), active methylene compound (**2**), barbituric acid (**3**) (2 mmol each) and 10 mol% 1,4-diazabicyclo[2,2,2]octane (DABCO) were taken in an RB flask with 15 ml solvent ethanol:water (1:1 ratio) mixture and stirred for 30–40 min at room temperature. The reaction was monitored by thin layer chromatography using eluent petroleum ether and ethyl acetate 7:3. The solid compound was filtered, washed with cold water and recrystallization from ethanol to obtain pure product pyrano[2,3-d]pyrimidine derivatives.

2.2. Spectral data for synthesized pyrano[2,3-d]pyrimidine products

2.2.1. Ethyl7-amino-5-(4-methylphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (**4a**)

IR (KBr, cm^{-1}): 3395, 3103, 2223, 1912, 1845, 1662, 1567, 1734, ^{1}H NMR (300 MHz, DMSO): δ 2.36 (s, 3H, CH3), 2.6 (s, 3H, CH$_3$), 4.13 (s, 1H, H-5), 5.21 (s, 2H, CH$_2$), 7.12 (m, 2H, H-Ar), 7.20 (m, 2H, H-Ar), 7.60 (br s, 2H, NH$_2$), 10.89 (s, 1H, NH), 11.43 (s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 20.9, 88.7, 98.3, 115.5, 127.5, 128.1,
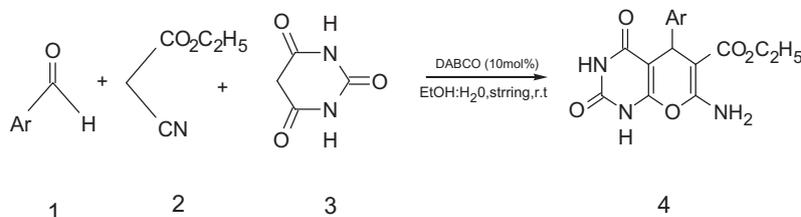
Scheme 1 General synthesis of substituted pyrano[2,3-d]pyrimidinones.
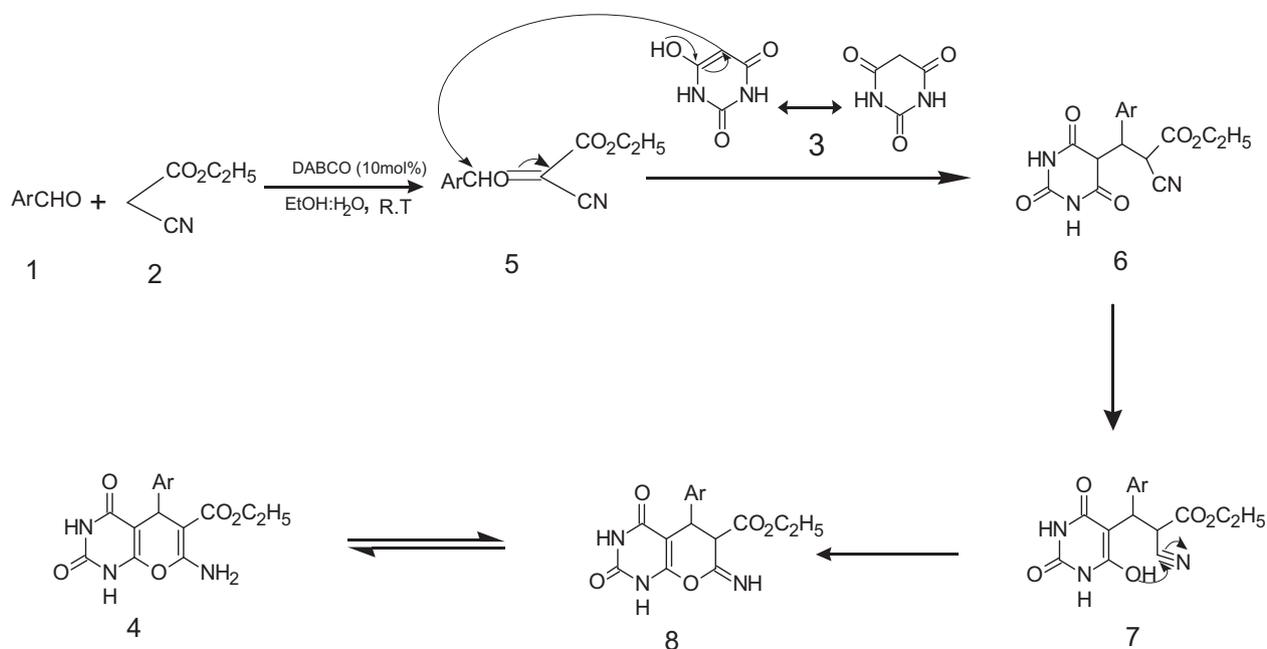
Scheme 2 Possible mechanism of pyrano[2,3-*d*]pyrimidine products.

133.7, 137.4, 150.1, 155.5,155.9 159.1, 159.9, 160.8, MS: (M +) *m/z*, 293, 292, 249, 77, 57, 43.

2.2.2. Ethyl 7-amino-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (4b)

IR (KBr, *v*cm^{-1}): 3381, 3168, 2289, 2202, 1664, 1708, 1560; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.6 (s, 3H, CH$_3$), 4.19 (s, 1H, H-5), 4.31 (s, 2H, CH$_2$), 6.07 (s, 1H, H-Ar), 7.10 (s, br, 2H, NH$_2$), 6.51–8.13 (m, 5H-Ar), 11.12 (br, s, 1H, NH), 12.14 (br, s, 1H, NH) PPm; ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 30.02, 60.2, 69.2, 128.6, 129.8, 135.4, 156.3, 152.8, ppm. EI-MS: (*m/z*) = 281 (M +), 256, 236, 205, 173, 141.

2.2.3. Ethyl 7-amino-5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrimidine-6-carboxylate (4c)

IR (KBr, *v* cm^{-1}): 3413, 3278, 2239, 2165, 1878, 1662, 1543; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.32 (s, 3H, OCH$_3$), 4.41 (1H, s, H-5), 3.71 (s, 2H, CH$_2$), 2.49 (s, 3H, CH$_3$) 6.93 (m, 2H, H-Ar), 7.65 (m, 2H, H-Ar), 9.07 (2H, br, s, NH$_2$), 11.09-10.03 (s, br, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 33.03, 37.2, 55.8, 75.6, 114.2, 130.1, 134.i, 143.9, 150.5, 157.2, 162.4, 167.3 ppm. EI-MS: (*m/z*) = 89 (M +), 269, 232, 221, 201, 176, 149, 110.

2.2.4. Ethyl7-amino-5-(3,4-dimethoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (4d)

IR (KBr, *v* cm^{-1}): 3495, 3303, 3123, 2987, 2164, 1662, 1576; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) δ: 3.12 (s, 3H, CH$_3$), 3.5 (s, 2H, CH$_2$), 3.6–4.02 (s, 3H, OCH$_3$), 4.2 (s, 1H, H-5), 7.1 (s, 2H, NH$_2$), 11.1 (s, 1H, NH), 11.4 (s, 1H, NH), 8.27 (m, 2H, H-Ar), 8.47 (m, 2H, H-Ar); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 37.9, 56.3, 57.4, 79.7, 114.2, 135.8, 146.9, 149.4, 150.1, 163.8 ppm. EI-MS: (*m/z*) = 342 (M +), 312, 295, 279, 249, 243, 220, 217, 149.

2.2.5. Ethyl 7-amino-5-(3-hydroxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (4e)

IR (KBr, *v* cm^{-1}):3439, 3337, 3193, 3028, 2206, 1677, 1625; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 3.6 (s, 3H, CH$_3$), 3.91 (s, 2H, CH$_2$), 4.10 (s, 1H, H-5), 6.56 (br s, 2H, NH$_2$), 6.59 (m, 1H, H-Ar), 7.04–7.10 (m, 3H, H-Ar), 9.33 (br s, 1H, OH), 11.09 (br s, 1H, NH), 12.07 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 35.6, 59.9, 89.5, 114.7, 114.9, 118.8, 120.1,130.1, 146.5, 150.4, 153.1, 158.1, 158.5, 163.3 ppm; MS: *m/z* (%) = 298 (M +), 249, 232, 188,142, 128, 115.

2.2.6. Ethyl7-amino-5-(4-hydroxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (4f)

IR (KBr, *v* cm^{-1}): 3343, 3191, 3142, 2209, 1909, 1796, 1685; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.69 (s, 1H, H-5), 3.17 (s, 2H, CH$_2$), 2.43 (s, 3H, CH$_3$), 7.31 (br s, 2H, NH$_2$), 5.97 (m, 2H, H-Ar), 6.74 (m, 2H, H-Ar), 6.07 (br s, 1H, OH), 10.47 (br s, 1H, NH), 11.03 (br s, 1H, NH) ppm: ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 29.03, 37.2, 61.5, 75.2, 79.9, 115.3, 134.4, 142.3, 150.4, 155.5, 160.1, 163.5 ppm. EI-MS: (*m/z*) = 298 (M +), 249, 232, 188, 142, 128, 115.

2.2.7. Ethyl7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (4g)

IR (KBr, cm^{-1}): 3311, 3188, 3091, 2228, 1899, 1648, 1543. ^{1}H NMR (100 MHz, DMSO-d_6, δ, ppm): 2.17 (3H, s, CH$_3$), 4.8 (2H, s, CH$_2$), 5.28 (s, 1H, H-5) 4.11(2H, s, CH$_2$), 2.29 (3H, s, CH$_3$), 7.28 (m, H-Ar), 7.38 (m, 2H, H-Ar), 7.75 (br s, 2H, NH$_2$), 10.99 (s, 1H, NH), 11.55 (s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 88.3, 98.5, 114.8, 126.9, 128.8, 129.0, 129.9, 130.5, 135.9, 150.1, 155.4, 155.8, 159.7, 160.9. MS: (M +) *m/z*, 313, 278, 188, 153, 111, 77, 57, 43.

2.2.8. Ethyl 7-amino-5-(4-bromophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (4h)

IR (KBr, v cm^{-1}): 3340, 3370, 3189, 3080, 2220, 1684, 1567; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 3.2 (s, 3H, CH$_3$), 3.8 (s, 2H, CH$_2$), 4.26 (s, 1H, H-5), 7.17 (s, 2H, NH$_2$), 7.20 (m, 2H, H-Ar), 7.48 (m, H-Ar), 12.45 (m, s, 1H, NH), 13.66 (m s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 35.3, 58.5, 82.8, 119.0, 120.0, 129.9, 132.2, 132.7, 143.0, 157.4, 160.3, 174.0 ppm.

2.2.9. Ethyl7-amino-5-(3-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (4i)

IR (KBr, v cm^{-1}): 3380, 3321, 3182, 2896, 1796, 1640, 1519; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.6(3H, s, CH$_3$), 4.1(2H, s, CH$_2$), 4.82 (s, 1H, H-5), 7.26 (s, 2H, NH$_2$), 7.52 (m, 2H, H-Ar), 8.14 (m, 2H, H-Ar), 11.12 (s, 1H, NH), 12.17 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 35.7, 57.5, 87.5, 119.0, 124.3, 130.7, 146.4, 149.6, 151.9, 152.7, 157.8, 162.6 ppm.

2.2.10. Ethyl 7-amino-5-(4-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (4j)

IR (KBr, v cm^{-1}): 3420, 3367, 3106, 2986, 1978, 1749,1604; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.92 (s, 1H, H-5), 7.26 (br s, 2H, NH$_2$), 7.32 (m, 2H, H-Ar), 8.09 (m, 2H, H-Ar), 9.67(s, 1H, NH), 10.15 (s, 1H, NH), 4.12 (s, 2H, CH$_2$), 3.09 (3H, s, CH$_3$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) δ: 37.2, 79.5, 61.7, 121.0, 130.0, 145.4, 148.3, 150.5, 160.3, 162.3, 163.8, 167.2 ppm.

3. Results and discussion

Herein we report a simple synthesis of annulated fused pyrano[2,3-d]pyrimidinones 4a–j as a domino Knoevenagel–Michael condensation. The experimental procedure is simple. Solutions of equimolar amounts of aromatic aldehyde 1, active methylene compound (ethylcyanoacetate) 2 and barbituric 3 in ethanol: water mixture at room temperature are mixed thoroughly in the presence of a catalytic amount of (10 mol%) DABCO (Scheme 1). It is imperative to point out here that the synthesis of pyrano[2,3-d]pyrimidine derivatives involves three components viz substituted aromatic aldehydes, barbituric acid and ethylcyanoacetate. We found that some

aromatic aldehydes and barbituric acid are not soluble in pure water solvent. Therefore time taken for consuming the reactants during the reaction is very high and yield of products is low under such conditions. Since, addition of a small amount of ethanol exhibited the complete solubility of key reactants like barbituric acid which is responsible for the formation of pyrano[2,3-d]pyrimidines in appropriate time with substantial yields. Hence, aqueous ethanol 15 ml (1:1 ratio) is employed as a better solvent compared to pure water in the synthesis of targeted/model products.

DABCO is bicyclo amine basic in character, so facilitates proton removal from active methylene compounds thereby increases reaction rate yields of annulated pyrano[2,3-d]pyrimidinones. We suggest that DABCO is an effective catalyst for the formation of the higher reactive iminium group which is utilized to facilitate Knoevenagel condensation between aryl aldehydes and active methylene compounds, which proceeds via intermediate, undergoes dehydration and finally heterocyclization to produce annulated pyrano[2,3-d]pyramidine derivatives. Table 1 shows the result of a series of representative aromatic aldehydes with active methylene compounds and barbituric acid to yield pyrano[2,3-d]pyrimidinones 4a–4j as sole products. DABCO catalyzed synthetic route is easy way to handle, non-corrosive in environmentally benign aqueous media, cheap, nontoxic and commercially available with advantageous high product's selectivity and yields. These formulated pyrano[2,3-d]pyrimidine products as biological agents may become excellent derivatives for globally alarming drug resistance issues in clinically used therapeutics. Table 2 shows the effect of different concentrations of catalyst for the synthesis of 4b in aqueous ethanol at room temperature and it was found 10 mol% of DABCO shows equal or more efficient catalytic activity in terms of reaction times and yields of the product. In the absence of the catalyst, the reaction was rather sluggish and resulted in poor yield (46%) even after 2.5 h time under same reaction conditions, thus confirming DABCO's role as an efficient catalyst. Catalyst gets easily removed by aqueous washing due to its solubility in water; hence no need of further neutralization and work-up is accomplished by simple filtration and recrystallization by ethanol. Prepared derivatives furnish a motivating model for studying the interaction of pyrano[2,3-d]pyrimidine with biological target as possible charge modification of substituent and O/N of pharmacophore groups present in skeleton. The presence of the heteroaryl ring, cyano, amino and different

Table 1 Synthesis of some pyrano[2,3-d]pyramidine derivatives.

Product	Ar	X	Color	Time (min)	Yield (%)[x]	M.P. (in °C)
4a	4-Me-C$_6$H$_4$	CO$_2$C$_2$H$_5$	White solid	40	87	296–298 [225][a]
4b	C$_6$H$_5$	CO$_2$C$_2$H$_5$	Yellow powder	35	94	206–210 [223][a]
4c	4-MeO-C$_6$H$_4$	CO$_2$C$_2$H$_5$	yellow powder	40	91	290–293 [297–298][b]
4d	3,4-MeO-C$_6$H$_4$	CO$_2$C$_2$H$_5$	Yellow powder	35	91	303–306 ——
4e	3-OH-C$_6$H$_4$	CO$_2$C$_2$H$_5$	Yellow solid	30	93	170–174 [161–163][c]
4f	4-OH-C$_6$H$_4$	CO$_2$C$_2$H$_5$	Yellow powder	40	94	163–167 ——
4g	4-Cl-C$_6$H$_4$	CO$_2$C$_2$H$_5$	White solid	40	86	295–300 [300][b]
4h	3-Br-C$_6$H$_6$	CO$_2$C$_2$H$_5$	White powder	40	84	235–237 [222–234][c]
4i	3-NO$_2$-C$_6$H$_4$	CO$_2$C$_2$H$_5$	White powder	35	82	237–240 [265][a]
4j	4-NO$_2$-C$_6$H$_4$	CO$_2$C$_2$H$_5$	White powder	30	83	289–293 [245][a]

[x] Yields refer to those of pure isolated products characterized by mass spectrometry and FTIR, ^{1}H and ^{13}C NMR spectroscopic data.
[a] Heravi et al. [15,16].
[b] Hamid et al. [14].
[c] Akbar et al.[1].

Table 2 **Optimization** mol% of DABCO during the synthesis of **4b** in aqueous ethanol.

Entry	Mole % of DABCO	Time (min)	Yield (%)[a]
1	5	40	81
2	10	40	94
3	15	35	73
4	20	45	70
5	30	30	62
6	40	30	54
7	No catalyst	2.5 h	46

[a] Isolated yield.

Table 3 Comparative synthesis of **4b** using N-type catalyst (DABCO) versus other catalysts.

Entry	Catalyst	Mole %	Solvent	Time (min)	Yield (%)[a]
1	Et$_3$N	2–3 drops	EtOH: H$_2$O	67	81
2	DBU	10 mol	EtOH: H$_2$O	54	78
3	Na$_2$CO$_3$	10 mol	EtOH: H$_2$O	95	69
4	NaOH	10 mol	EtOH: H$_2$O	127	64
5	K$_2$CO$_3$	10 mol	EtOH: H$_2$O	105	57
6	DABCO	10 mol	EtOH: H$_2$O	35	94 (Present work)

[a] Isolated yields.

substituents viz: methyl, hydroxyl, methoxy, nitrile and bromile groups on the pyranopyramidine ring makes these more active for biological evolution. Future flexible pharmacophore site geometric conformation enables to prepare derivatives for multi-therapeutic pyrano[2, 3-d]pyrimidine products with high selectivity.

Further, we have worked on systematic evaluation of different catalysts for the model reaction of benzaldehyde, ethyl-cyanoacetate and barbituric acid using aqueous ethanol 15 ml (1:1 ratio) as solvent (Table 3). We found that yield of model product **4b** (see manuscript Table 1) is 94% using N-type DABCO catalyst as compared to the other various catalysts such as Et$_3$N, DBU, Na$_2$CO$_3$, NaOH, K$_2$CO$_3$ which is only 57–81%. These results indicated that time taken for the synthesis of model product **4b** using DABCO is only 35 min as compared to other catalysts viz Et$_3$N, DBU, Na$_2$CO$_3$, NaOH, K$_2$CO$_3$ which is more 54–127 min (Table 3). We have found that due to more addition of Et$_3$N and DBU catalysts the product formation is very low and the removal of catalysts by simple washing is very difficult. The synthesis of pyrano[2,3-*d*]pyrimidines is based on two step mechanism such as Knoevenagel–Michael addition reaction. The catalysts like Et$_3$N, DBU, Na$_2$CO$_3$, NaOH, K$_2$CO$_3$ and other catalysts do not show good results for the synthesis of targeted/model **4b** compound and such catalysts work more efficiently only in simple Knoveangel condition [4,22,25,28,31]. The Michael addition of barbituric acid on the synthesized arylidene and the heterocyclization as well as dehydration is not much favorable by using such catalysts due to the presence of the heteroaryl ring, cyano, amino and different substituent groups on the pyranopyrimidine ring. Therefore, we used DABCO as an efficient N-type catalyst as compared to the other various organic and inorganic catalysts for one–pot three component synthesis of pyrano[2,3-*d*]pyrimidine derivatives.

4. Conclusions

In conclusion we have developed a rapid and an efficient synthetic route for DABCO catalyzed one-pot three component synthesis of annulated fused pyrano[2,3-*d*]pyrimidines in aqueous ethanol at room temperature and the current synthetic route has the advantages of operational simplicity, mild reaction conditions and good to high yield of the biological active products. Our method is simple as no special apparatus, reagents or chemicals, for work up are required, and the compound formed is filtered and purified just by simple crystallization. This synthesis is also advantageous in terms of atom economy as well as is devoid of any hazardous chemicals.

References

[1] M. Akbar, F. Naser, A.B. Mohammad, Eco-friendly and efficient synthesis of pyrano[2,3-*d*] pyrimidinone and tetrahydrobenzo[b]pyran derivatives in water. Synthesis and reactivity in inorganic, metal-organic, and nano-metal, Chemistry 40 (2010) 179–185.

[2] G.L. Anderson, J.L. Shim, A.D. Broom, Pyrido[2,3-*d*]pyrimidines. IV. Synthetic studies leading to various oxopyrido[2,3-*d*]pyramidine, J. Org. Chem. 41 (1976) 1095.

[3] S. Balalaie, S.H. Abdolmohammadi, H.R. Bijanzadeh, M. Amani, Diammonium hydrogen phosphate as a versatile and efficient catalyst for the one-pot synthesis of pyrano[2,3-*d*]pyrimidinone derivatives in aqueous media, Mol. Diver. 12 (2008) 85–91.

[4] D. Bandita, A.P. Mohamed, I$_2$/K$_2$CO$_3$: an efficient catalyst for the synthesis of 5-aryl-2,6-dicyano-3-methylanilines, J. Chem. Sci. 125 (2) (March 2013) 291–294.

[5] M. Bararjanian, S. Balalaie, B. Movassagh, A.M. Amani, One-pot synthesis of pyrano[2,3-*d*]pyrimidinone derivatives catalyzed by L-proline in aqueous media, J. Iran. Chem. Soc. 6 (2009) 436–442.

[6] L.R. Bennett, C.J. Blankely, R.W. Fleming, R.D. Smith, D.K. Tessonam, Antihypertensive activity of 6-arylpyrido[2,3-*d*]pyrimidin-7-amine derivatives, J. Med. Chem. 24 (1981) 382.

[7] C. Castello, B. List, A novel proline-catalyzed three-component reaction of ketones, aldehydes, and meldrum's acid, Synlett (2001) 1687–1689.

[8] Chao-Jun Li, Organic reactions in aqueous media – with a focus on carbon–carbon bond formation, Chem. Rev. 93 (1993) 2023.

[9] J. Davoll, J. Clarke, F.E. Eislager, Antimalarial, antagonists, antimalarial and antimetabolite effects of 2,4-diamino-6-[(benzyl)amino]pyrido[2,3-*d*]pyrimidines, J. Med. Chem. 15 (1972) 837.

[10] I. Devi, Kumar, P.J. Bhuyan, A novel three-component one-pot synthesis of pyrano[2,3-*d*]pyrimidines and pyrido[2,3-*d*]pyrimidines using microwave heating in the solid state, Tetrahedron Lett. 44 (2003) 8307–8310.

[11] P.A. Grieco, Organic Synthesis in Water, Thomson Science, Glasgow, 1998, 1-80, 250-261.

[12] E.M. Grivsky, S. Lee, C.W. Sigel, D.S. Duch, C.A. Nichol, Synthesis and antitumor activity of 2,4-diamino-6-(2,5-dimethoxybenzyl)-5- methylpyrido[2,3-d]pyrimidine, J. Med. Chem. 23 (1980) 327–329.

[13] Y. Gao, S. Tu, T. Li, X. Zhang, S. Zhu, F. Fang, D. Shi, Effective synthesis of 7-amino-6-cyano-5-aryl-5H-pyrano[2,3-d]pyrimidine-2,4(1H,3H)-diones under microwave irradiation, Synth. Commun. 34 (2004) 1295–1299.

[14] R.S. Hamid, S. Mohsen, R. Sudabeh, S. Athar, Glycerol as a biodegradable and reusable promoting medium for the catalyst-free one-pot three component synthesis of 4H-pyrans, Green Chem. 14 (2012) 1696.

[15] M.M. Heravi, A. Ghods, K. Bakhtiari, F. Derikvand, Zn[(L)proline]2: an efficient catalyst for the synthesis of biologically active pyrano[2,3-d]pyrimidine derivatives, Synth. Commun. 40 (2010) 1927–1931.

[16] M.M. Heravi, A. Ghods, F. Derikv, K. Bakhtiari, F.F. Bamoharram, H14[NaP5W30O110] catalyzed one-pot three-component synthesis of dihydropyrano[2,3-c]pyrazole and pyrano[2,3-d]pyrimidine derivatives, J. Iran. Chem. Soc. 7 (2010) 615–620.

[17] D. Heber, C. Heers, U. Ravens, Positive inotropic activity of 5-amino-6-cyano-1,3-dimethyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione in cardiac muscle from guinea-pig and man. Part 6: compounds with positive inotropic activity, Die Pharmazie 48 (1993) 537–541.

[18] T.S. Jin, L.B. Liu, S.J. Tu, Y. Zhao, T.S. Li, Clean one-pot synthesis of 7-amino-5-aryl-6-cyano-1,5-dihydro-2H-pyrano [2,3-d]pyrimidine-2,4(3H)-diones in aqueous media under ultrasonic irradiation, J. Chem. Res. 3 (2005) 162–163.

[19] G. Kaupp, Reactions in supercritical carbon dioxide, Angew. Chem. 106 (1994) 1519–1522.

[20] E. Kretzschmer, Pharmazie 35 (1980) 253.

[21] A. Lubineau, J. Auge, Y. Queneau, Water-promoted organic reactions, Synthesis 741 (1994) 1998.

[22] W. Madhav, M. Balaji, P. Rajkumar, K. Gopal, S. Murlidhar, DBU: an efficient catalyst for Knoevenagel condensation under solvent free condition, Bull. Catal. Soc. India 6 (2007) 104–106.

[23] J.O. Metzger, Solvent-free organic syntheses, Angew. Chem. Int. Ed. Engl. 37 (1998) 2975.

[24] C. Musstazza, M.R.D. Guidice, A. Borioni, F. Gatta, Synthesis of pyrazolo[1,5-a]-,1,2,4-triazolo[1,5-a]- and imidazo[1,2-a]pyrimidines related to zaleplon, a new drug for the treatment of insomni, J. Heterocycl. Chem. 38 (2001) 1119–1130.

[25] M.A. Pasha, M. Krishnappa, V.P. Jayashankara, Sodium carbonate: a versatile catalyst for Knoeveneagel condensation, Indian J. Chem. 49B (2010) 1428–1431.

[26] Y. Sakuma, M. Hasegawa, K. Kataoka, K. Hoshina, N. Kadota, 1,10-Phenanthroline derivatives, Chem. Abstr. 115 (1991) 71646.

[27] A.H. Shamroukh, M.E.A. Zaki, E.M.H. Morsy, F.M. AbdelMotti, F.M.E. AbdelMegeid, Synthesis of pyrazolo[4,3:5,6]pyrano[2,3-d]pyramidine derivatives for antiviral evaluation, Arch. Pharm. 340 (2007) 236–243.

[28] S.Al.-S. Shar, Synthesis of substituted stilbenes via the Knoevenagel condensation, Molecules 9 (2004) 658–665.

[29] A.M. Shestopalov, Y.M. Emeliyanova, L.A. Rodinovskaya, Z.I. Niazimbetova, D.H. Evans, One-step synthesis of substituted 6-amino-5 cyanospiro-4-(piperidine-4)-2H, 4H-dihydropyrazolo [3,4-b]pyrans, Org. Lett. 4 (2002) 423–425.

[30] S. Shigo, I. Hiroshi, Y. Zasshi, 89 (1969), 266.

[31] G. Thirupathi, M. Venkatanarayana, P.K. Dubey, K.Y. Bharathi, L-tyrosine catalyzed Knoevenagel condensation: facile synthesis of cyanoacrylonitriles cyanoacrylates and cyanoacrylamides in solvent free condition under grindstone method, Der Pharma Chem. 4 (5) (2012) 1897–1901.

[32] L. Weber, K. Illegel, M. Almstetter, Discovery of new multi component reactions with combinatorial method, Synlett (1999) 366–374.

[33] J. Yu, H. Wang, Green synthesis of pyrano[2,3-d]-pyrimidine derivatives in ionic liquids, Synth. Commun. 35 (2005) 3133–3140.

[34] G.M. Ziarani, A. Faramarzi, S. Asadi, A. Badiei, R. Bazl, M. Amanlou, Three-component synthesis of pyrano[2,3-d]-pyrimidine dione derivatives facilitated by sulfonic acid nanoporous silica (SBA-Pr-SO3H) and their docking and urease inhibitory activity, DARU J. Pharm. Sci. 21 (2013) 3, http://dx.doi.org/10.1186/2008-2231-21-3.